National Addiction Centre

Institute of Psychiatry at The Maudsley

King's College London

Concentrated naloxone nasal spray for opioid overdose reversal:

Pharmacokinetic study in healthy volunteers

John Strang & Rebecca McDonald

Declarations (personal & institutional)

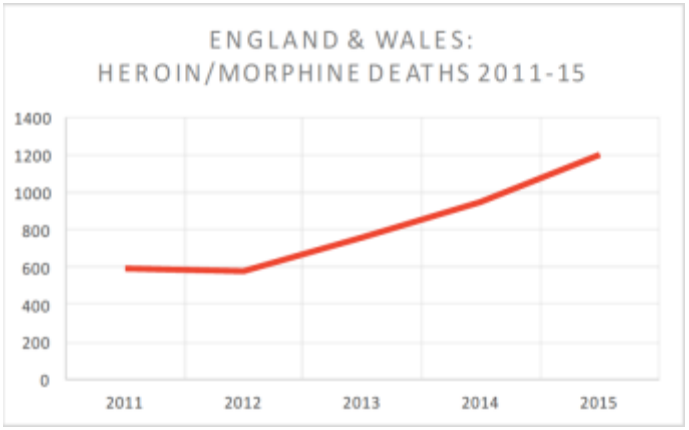
- NHS provider; also Phoenix House, Lifeline, Clouds House, KCA.
- Collaboration with and support from charities: incl. Action on Addiction, J Paul Getty Charitable Trust (JPGT) and Pilgrim Trust.
- Society for the Study of Addiction (SSA); UKDPC (UK Drug Policy Commission), and two Master's degrees (taught MSc and IPAS) and an Addictions MOOC at KCL.
- Dialogue and work with pharmaceutical companies to seek to identify new or improved treatments (including naloxone products), including (past 3 years): Martindale, Indivior, Mundipharma, Braeburn; trial product supply from iGen.
- Mundipharma Research Ltd.:
  - JS named as inventor in a patent application filed in 2011 by an independent associated company of Mundipharma
  - funding to KCL for JS' time and input
  - RM – PhD student industry placement, with focus on analysis of study presented today.
- KCL has separately registered intellectual property on a novel buccal naloxone formulation with which JS and RM are involved
- DH, NTA, Home Office; NACD, NIDA; EMCDDA, WHO, UNODC (also RM).

Overview

1. **Background: opioid overdose deaths, need for non-injectable naloxone, and feasibility of nasal route**
2. New nasal study - Methods: PK in healthy volunteers
3. New nasal study - Key findings
4. Implications for clinical practice and policy

1 | Background - UK

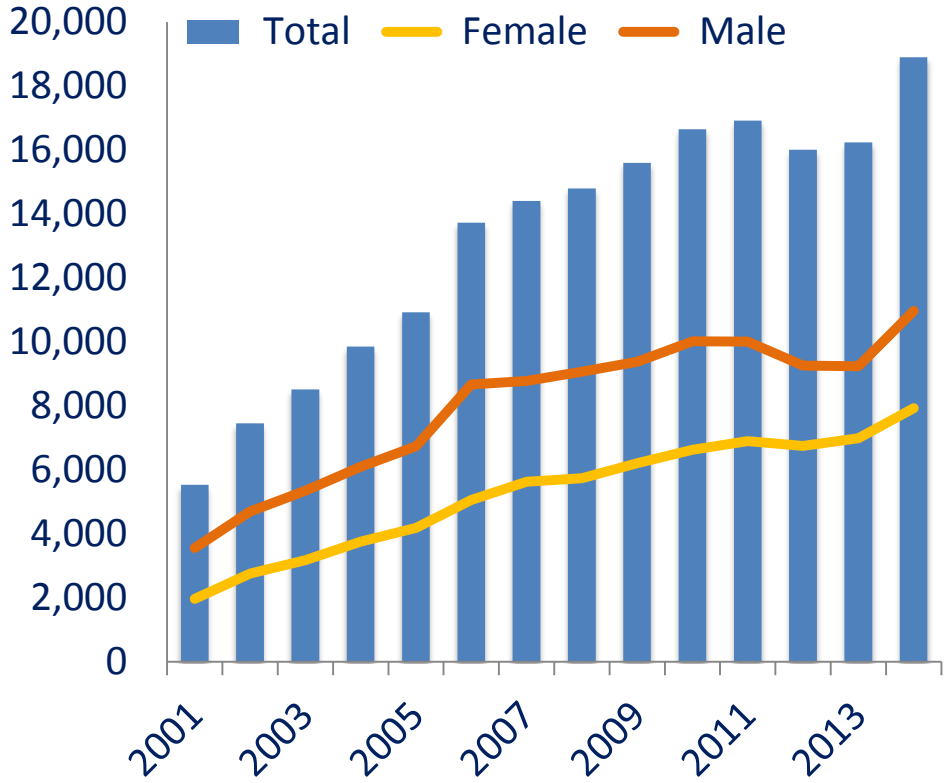
- Opioid use = int'l public health problem (UNODC/WHO 2013)
- UK heroin/morphine deaths 2011-15:
  - England & Wales: ↑ 102% (ONS, 2016)
  - Scotland: ↑ 68% (NRS, 2016)
- Take-home naloxone since 1996 (Bigg 2002; Strang et al 1996)
- 2014 WHO Guidelines

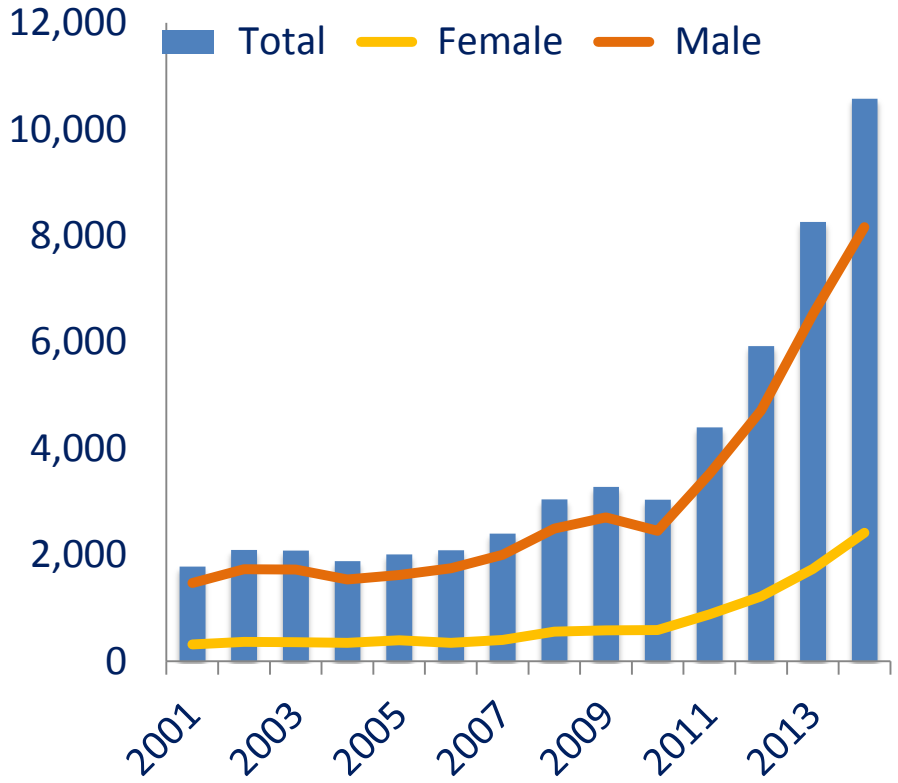


National Institute on Drug Abuse

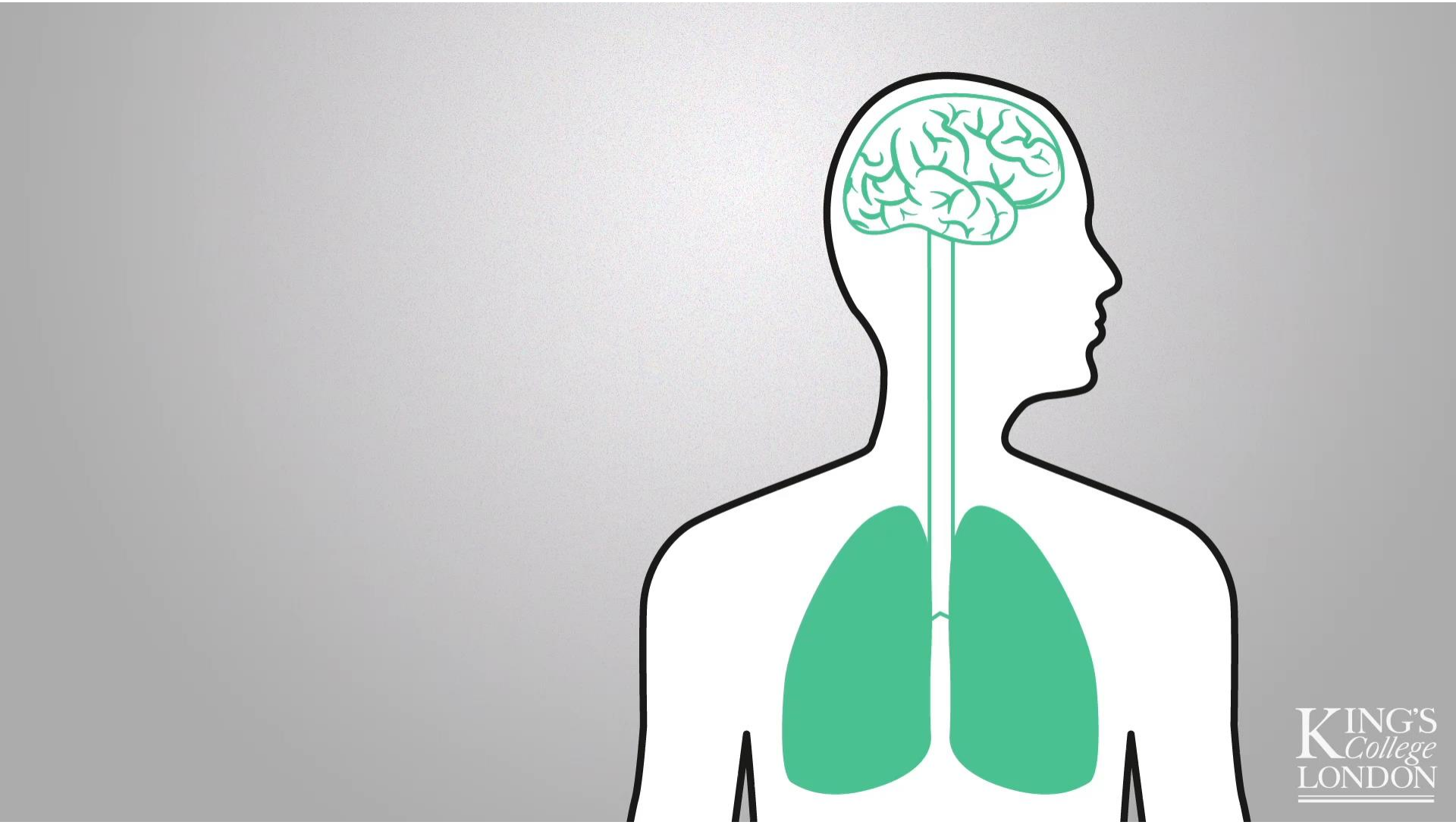
1 | Overdose Deaths in the US

Number of Deaths from (a) Prescription Opioids & (b) Heroin





National Center for Health Statistics (2014). *CDC Wonder*.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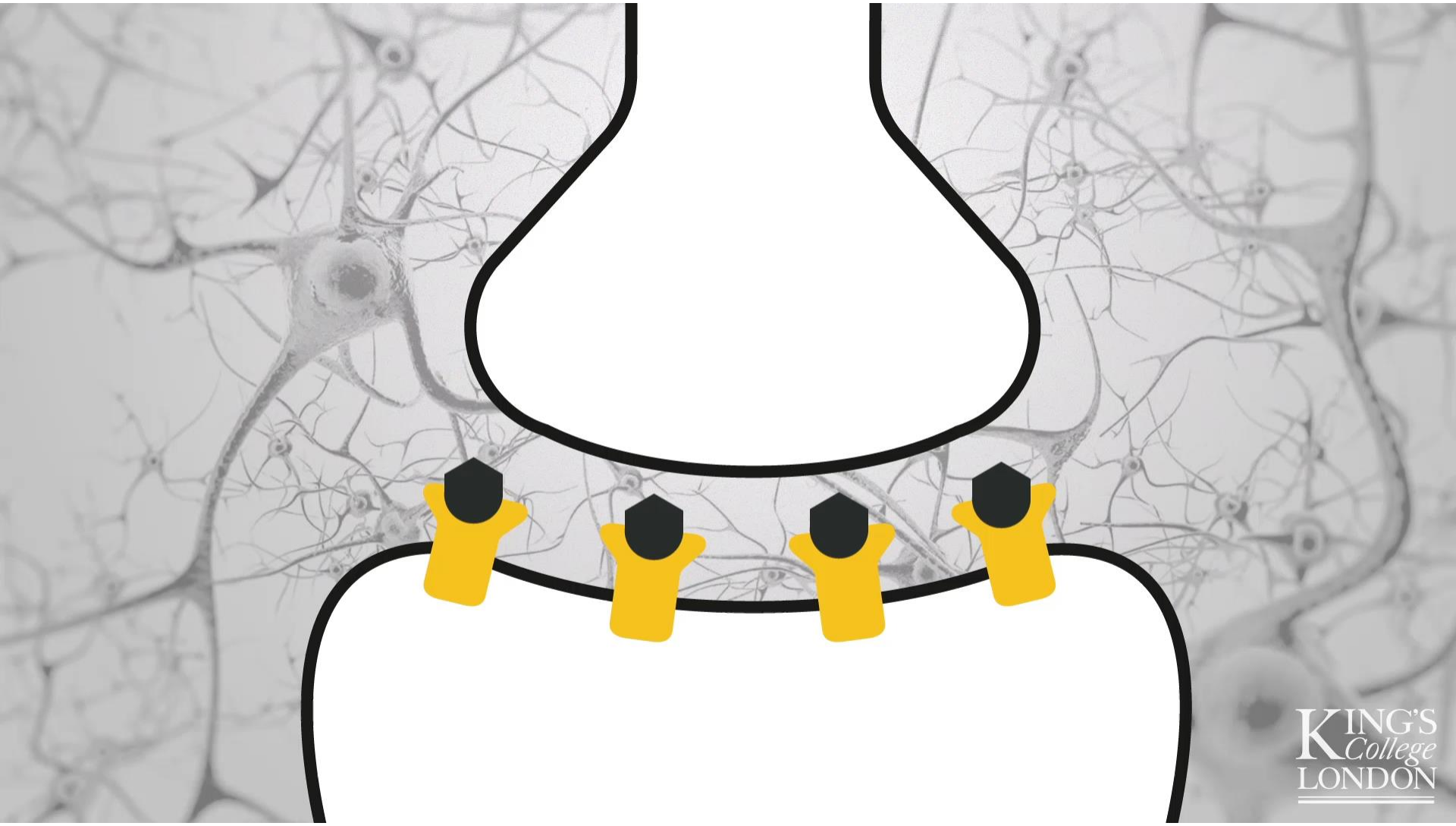
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Community management of opioid overdose

Recommendation

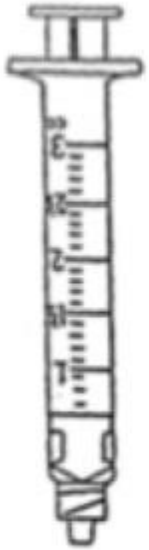
People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose.

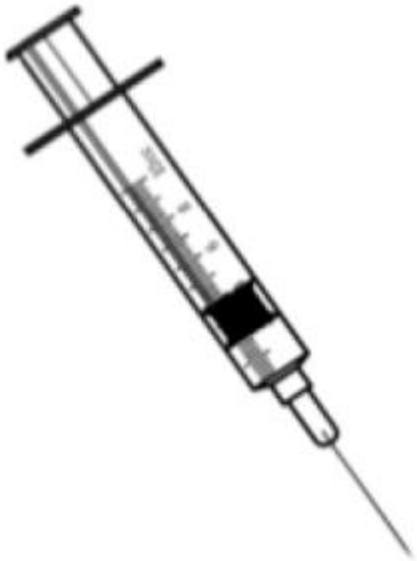
World Health Organization

WHO (2014). *Community Management of Opioid Overdose.* Geneva: WHO.

All work

None perfect





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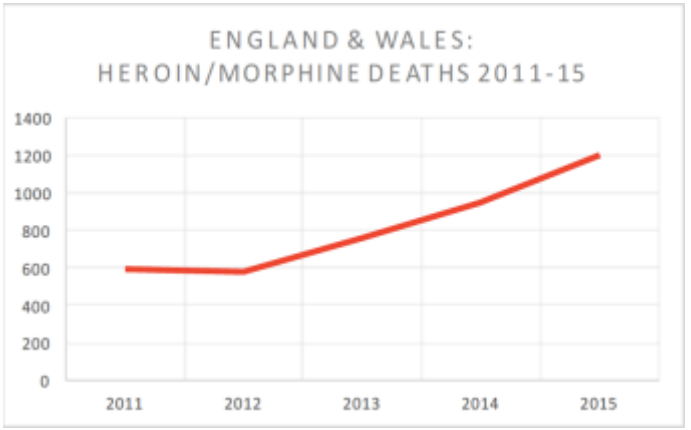

But: Naloxone = injection

- Risk of needle-stick injury
- Training required; taboo to be overcome
- Reticence about needle-and-syringe assembly and injecting
- Public disquiet; professional inertia
- Institutional inertia

1.1 | Identification of non-injectable routes

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Review

Naloxone without the needle – systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal

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ABSTRACT

Introduction: Deaths from opioid overdose can be prevented through administration of the antagonist naloxone, which has been licensed for injection since the 1970s. To support wider availability of naloxone in community settings, novel non-injectable naloxone formulations are being developed, suitable for emergency use by non-medical personnel.
Objectives: 1) Identify candidate routes of injection-free naloxone administration potentially suitable for emergency overdose reversal; 2) consider pathways for developing and evaluating novel naloxone formulations.
Methods: A three-stage analysis of candidate routes of administration was conducted: 1) assessment of all 112 routes of administration identified by FDA against exclusion criteria. 2) Scrutiny of empirical data for identified candidate routes, searching PubMed and WHO International Clinical Trials Registry Platform using search terms "naloxone AND [route of administration]". 3) Examination of routes for feasibility and against the inclusion criteria.
Results: Only three routes of administration met inclusion criteria: nasal, sublingual and buccal. Products are currently in development and being studied. Pharmacokinetic data exist only for nasal naloxone, for which product development is more advanced, and one concentrated nasal spray was granted licence in the US in 2015. However, buccal naloxone may also be viable and may have different characteristics.
Conclusion: After 40 years of injection-based naloxone treatment, non-injectable routes are finally being developed. Nasal naloxone has recently been approved and will soon be field-tested, buccal naloxone holds promise, and it is unclear what sublingual naloxone will contribute. Development and approval of reliable non-injectable formulations will facilitate wider naloxone provision across the community internationally.

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Strang, J., McDonald, R., Alqurshi, A., Royall, P., Taylor, D., & Forbes, B. (2016). Naloxone without the needle− systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal. *Drug and Alcohol Dependence*, *163*, 16-23.

1.1 | Identification of non-injectable routes

- Review of 112 FDA-recognized routes of drug administration (FDA, 1992)

- Exclusion if the route…
  1. Involves injection or invasive procedure
  2. Requires medical training
  3. Is not acceptable in public (e.g., rectal)
  4. Does not produce adequate drug absorption
  5. Does not produce sufficiently rapid drug absorption relative to parenteral administration (Hertz, 2012)

Strang, J., McDonald, R., Alqurshi, A., Royall, P., Taylor, D., & Forbes, B. (2016). Naloxone without the needle− systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal. *Drug and Alcohol Dependence*, *163*, 16-23.

1.1 | Identification of non-injectable routes

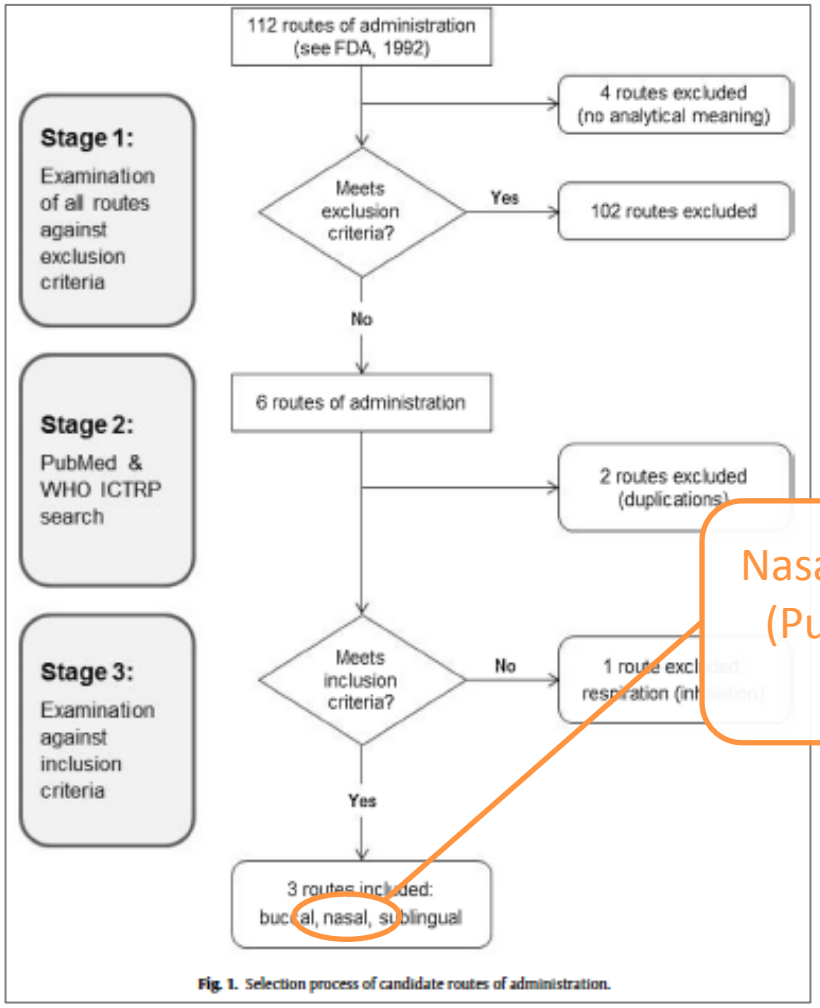

Fig. 1. Selection process of candidate routes of administration.

Nasal route most advanced (PubMed entries, clinical trials activity)

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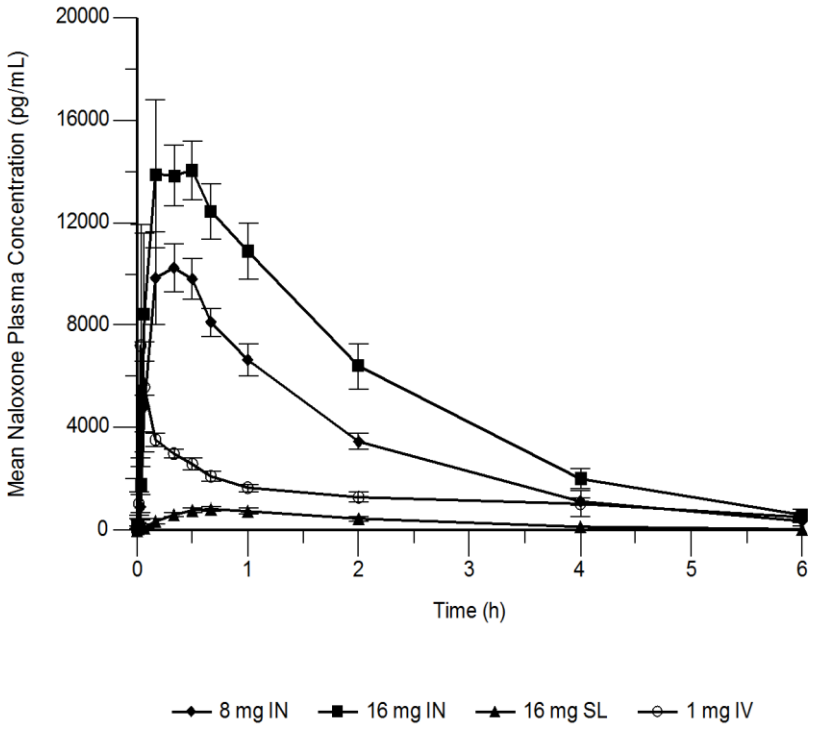
1.2 | Why a KCL-Mundipharma collaboration?

- **Serendipitous discovery and retrieval of 2004 dataset of pharmacokinetic study conducted in US by Purdue**
  - Original aim: assess abuse liability of oxycodone-naloxone formulation
  - Healthy volunteers (n=12)
  - Latin square design:
    - 1mg IV vs. 16mg SL vs. 8mg IN vs. 16mg IN

- **Our aim: Suitability of nasal naloxone for OD reversal?**
  - Darke & Duflou (2016): heroin OD death occurred within 20-30 minutes of injecting in 43% of cases
  - Naloxone concentrated solutions
  - Naloxone absorption in first 30 minutes crucial

1.2 | New analysis of old data



Mundin, McDonald et al. (submitted). *Pharmacokinetics of concentrated naloxone nasal spray over first 30 minutes post-dosing: analysis of suitability for opioid overdose reversal.*

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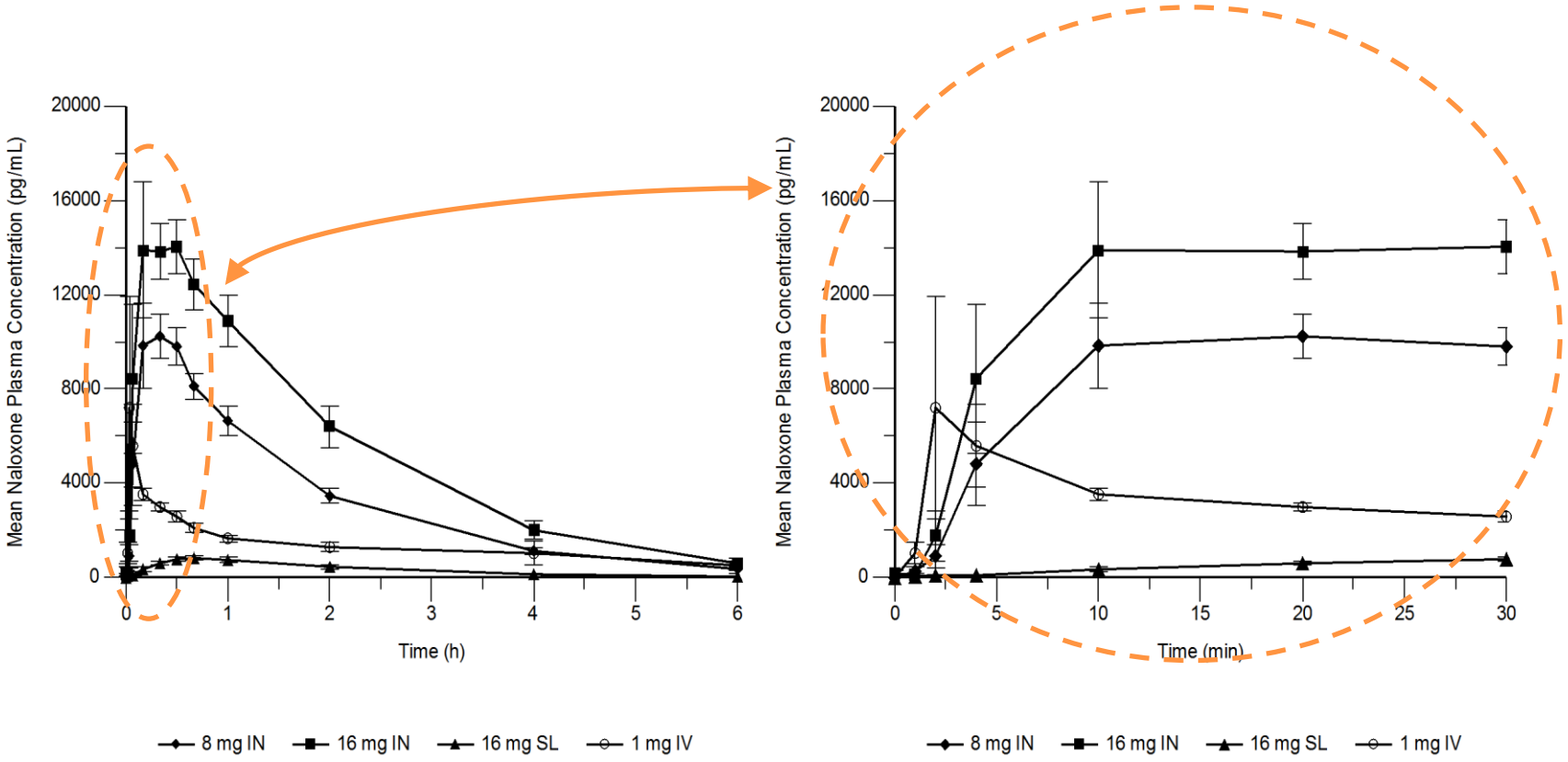

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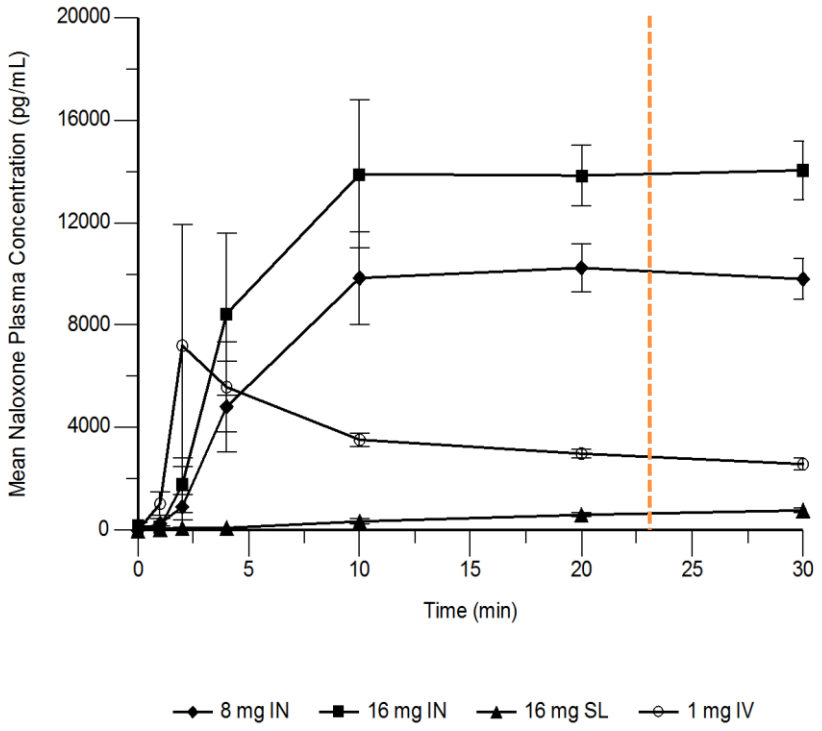
1.2 | New analysis of old data

Tmax = 23 min



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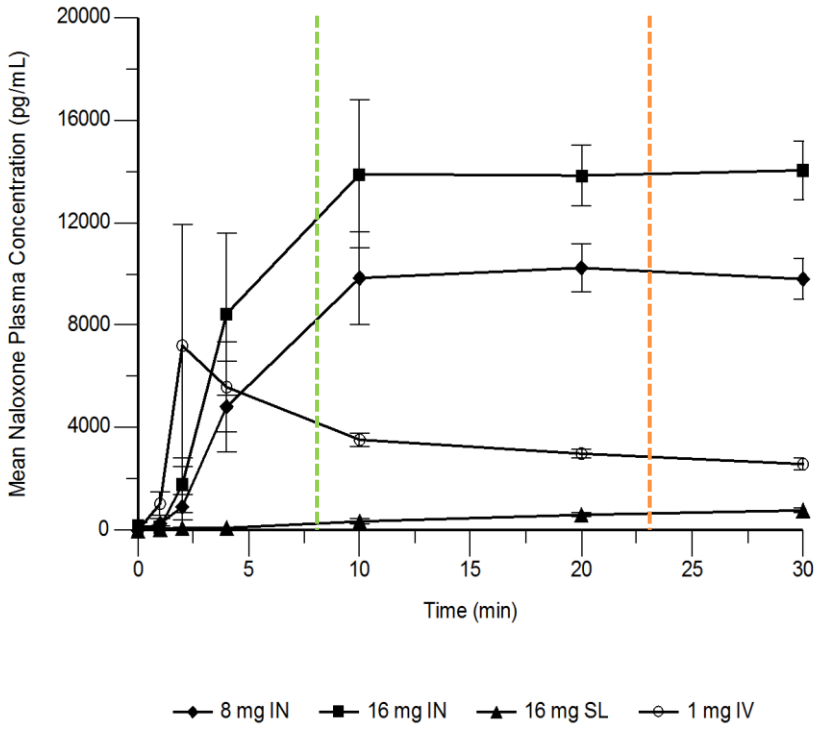
1.2 | New analysis of old data

Tmax = 23 min
T50% = 7-8 min



Mundin, McDonald et al. (submitted). *Pharmacokinetics of concentrated naloxone nasal spray over first 30 minutes post-dosing: analysis of suitability for opioid overdose reversal.*

1.2 | New analysis of old data - conclusion

- Key points:
  1. Feasibility of concentrated nasal naloxone for OD reversal
  2. Rapid absorption (Tmax and T50%)
  3. **But:** dose needs adjustment!

Mundin, McDonald et al. (submitted). *Pharmacokinetics of concentrated naloxone nasal spray over first 30 minutes post-dosing: analysis of suitability for opioid overdose reversal.*

Injection-free Alternatives

Pharmacokinetics

Pharmacokinetic Properties and Human Use Characteristics of an FDA-Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose

The Journal of Clinical Pharmacology
2016, 00(0) 1–11
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DOI: 10.1002/jcph.759

(2016)

Philip Krieter, PhD[1], Nora Chiang, PhD[1], Shwe Gyaw, MD[1], Phil Skolnick, PhD, DSc (hon)[1], Roger Crystal, MD[2], Fintan Keegan, MSc[3], Julie Aker, MT (ASCP)[4], Melissa Beck, BA[4], and Jennifer Harris, BA[4]

Abstract

Parenteral naloxone has been approved to treat opiate overdose for over 4 decades. Intranasal naloxone, administered "off label" using improvised devices, has been widely used by both first responders and the lay public to treat overdose. However, these improvised devices require training for effective use, and the recommended volumes (2 to 4 mL) exceed those considered optimum for intranasal administration. The present study compared the pharmacokinetic properties of intranasal naloxone (2 to 8 mg) delivered in low volumes (0.1 to 0.2 mL) using an Aptar Unit-Dose device to an approved (0.4 mg) intramuscular dose. A parallel study assessed the ease of use of this device in a simulated overdose situation. All doses of intranasal naloxone resulted in plasma concentrations and areas under the curve greater than those observed following the intramuscular dose; the time to reach maximum plasma concentrations was not different following intranasal and intramuscular administration. Plasma concentrations of naloxone were dose proportional between 2 and 8 mg and independent of whether drug was administered to 1 or both nostrils. In a study using individuals representative of the general population, >90% were able to perform both critical tasks (inserting nozzle into a nostril and pressing plunger) needed to deliver a simulated dose of naloxone without prior training. Based on both pharmacokinetic and human use studies, a 4-mg dose delivered in a single device (0.1 mL) was selected as the final product. This product can be used by first responders and the lay public, providing an important and potentially life-saving intervention for victims of an opioid overdose.

Krieter, P., Chiang, N., Gyaw, S., Skolnick, P., Crystal, R., Keegan, F., ... & Harris, J. (2016). Pharmacokinetic Properties and Human Use Characteristics of an FDA-Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose. *The Journal of Clinical Pharmacology*.

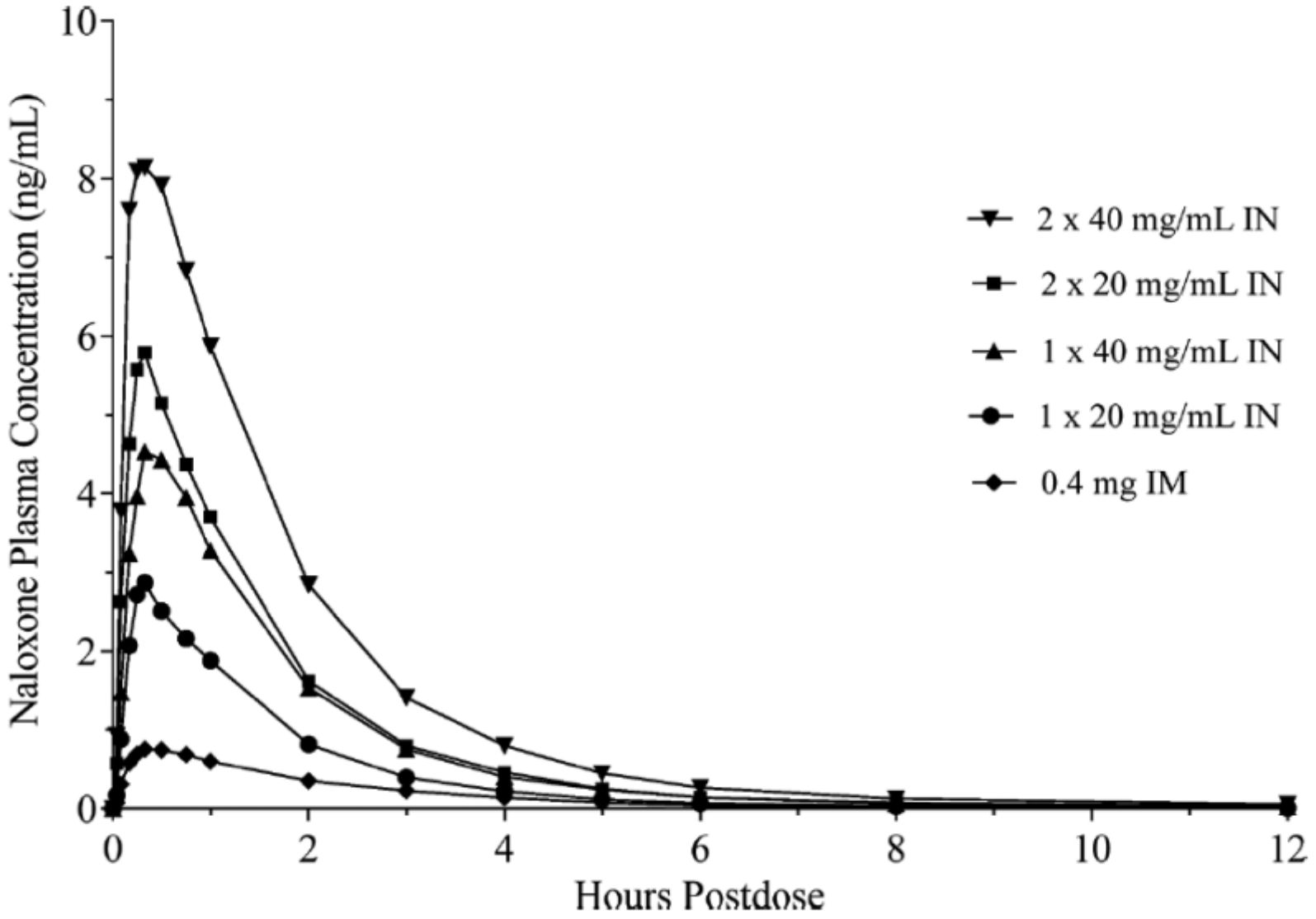


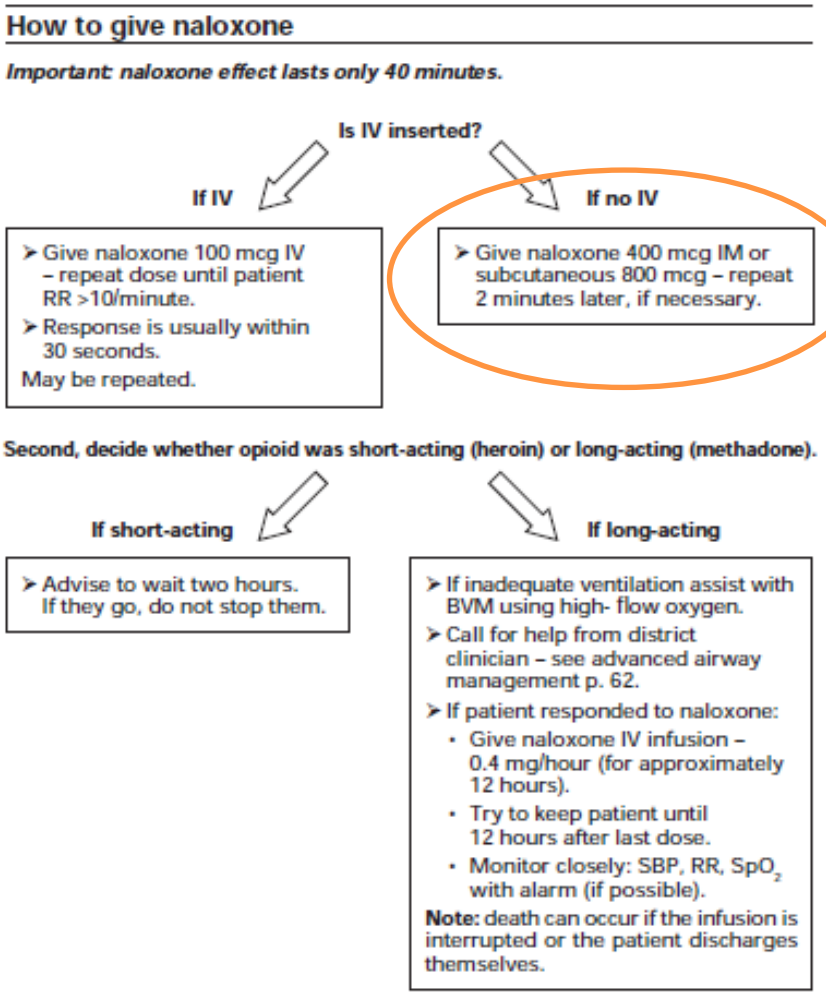
Figure 2. Plasma concentrations of naloxone following intranasal and intramuscular administration of naloxone HCl. Twenty-eight subjects were randomized in a 5-period, 5-treatment, 5-sequence crossover study, receiving 1 or 2 doses (0.1 mL per nostril) of a naloxone HCl formulation (20 and 40 mg/mL) or an intramuscular injection of 0.4 mg. IN, intranasal; IM, intramuscular.

Overview

1. Background: opioid overdose deaths, need for non-injectable naloxone, and feasibility of nasal route
2. **New nasal study - Methods: PK in healthy volunteers**
3. New nasal study - Key findings
4. Implications for clinical practice and policy

The new study

2.1 | Development and study of a new naloxone nasal spray for overdose reversal



How to give naloxone

Important: naloxone effect lasts only 40 minutes.

Is IV inserted?

If IV

- Give naloxone 100 mcg IV – repeat dose until patient RR >10/minute.
- Response is usually within 30 seconds.

May be repeated.

If no IV

- Give naloxone 400 mcg IM or subcutaneous 800 mcg – repeat 2 minutes later, if necessary.

Second, decide whether opioid was short-acting (heroin) or long-acting (methadone).

If short-acting

- Advise to wait two hours. If they go, do not stop them.

If long-acting

- If inadequate ventilation assist with BVM using high- flow oxygen.
- Call for help from district clinician – see advanced airway management p. 62.
- If patient responded to naloxone:
  - Give naloxone IV infusion – 0.4 mg/hour (for approximately 12 hours).
  - Try to keep patient until 12 hours after last dose.
  - Monitor closely: SBP, RR, SpO_2 with alarm (if possible).

Note: death can occur if the infusion is interrupted or the patient discharges themselves.

WHO (2011). *IMAI district clinician manual: hospital care for adolescents and adults: guidelines for the management of illnesses with limited-resources.* Geneva: WHO.

2.2 | Methods: Randomised pharmacokinetic study

- Design: open-label, 5-way crossover
- Healthy volunteers (n=36)
- Investigational site: Richmond Pharmacology
- Highly concentrated naloxone (10, 20 mg/mL)
- IN naloxone as 0.1ml in Aptar device
- Treatment arms:
  - 1mg IN vs. 2mg IN vs. 4mg IN vs. 0.4mg IV vs. 0.4mg IM (reference)
- Early uptake: intense blood sampling 0-15 min (+1, 2, 3, 4, 6, 8, 10, 12.5, 15 min)

- **Aims:**
  1. Assess IN naloxone PK
  2. Compare early exposure vs. IM

Overview

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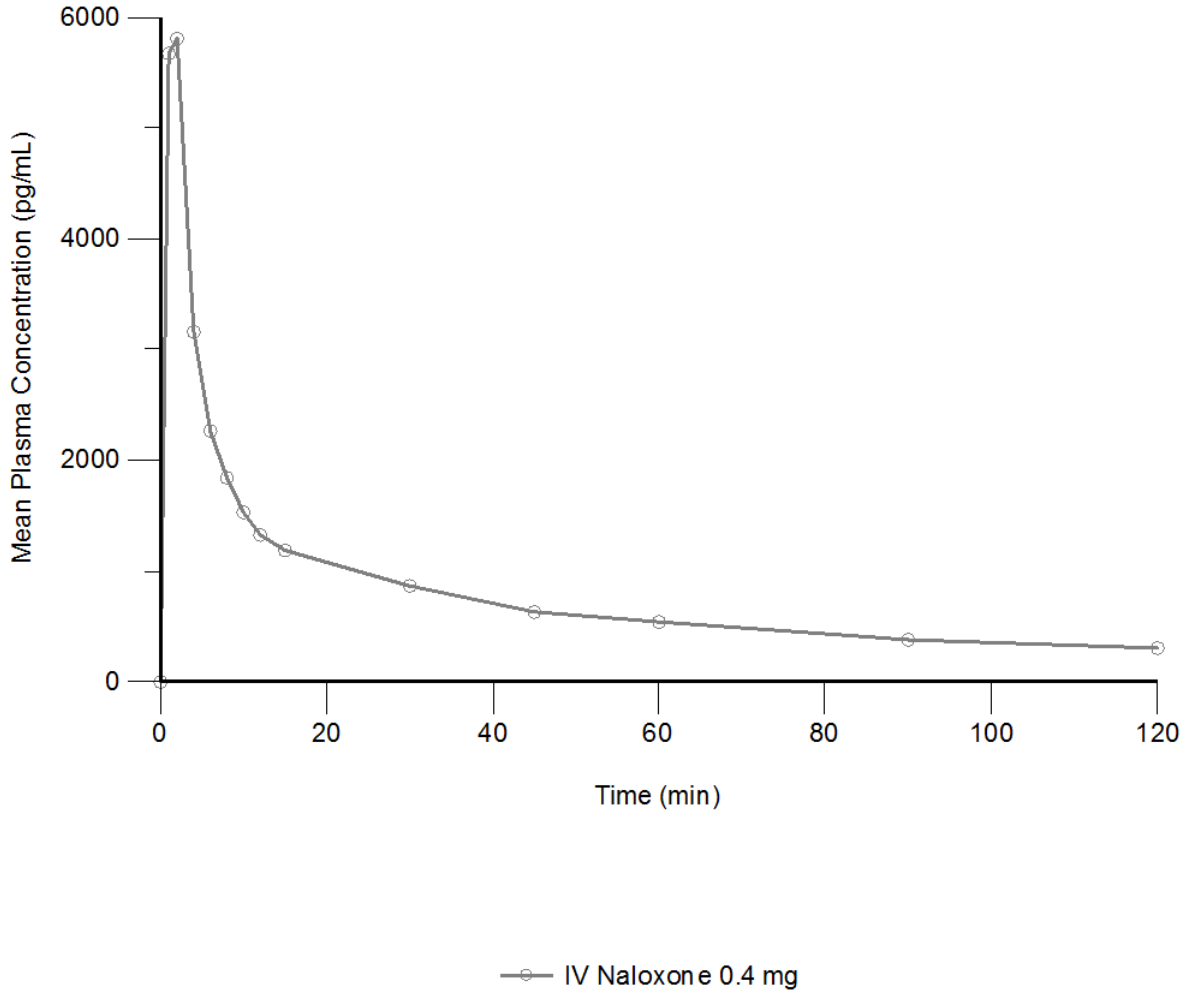
3.1 | Key findings: Naloxone mean PK profile



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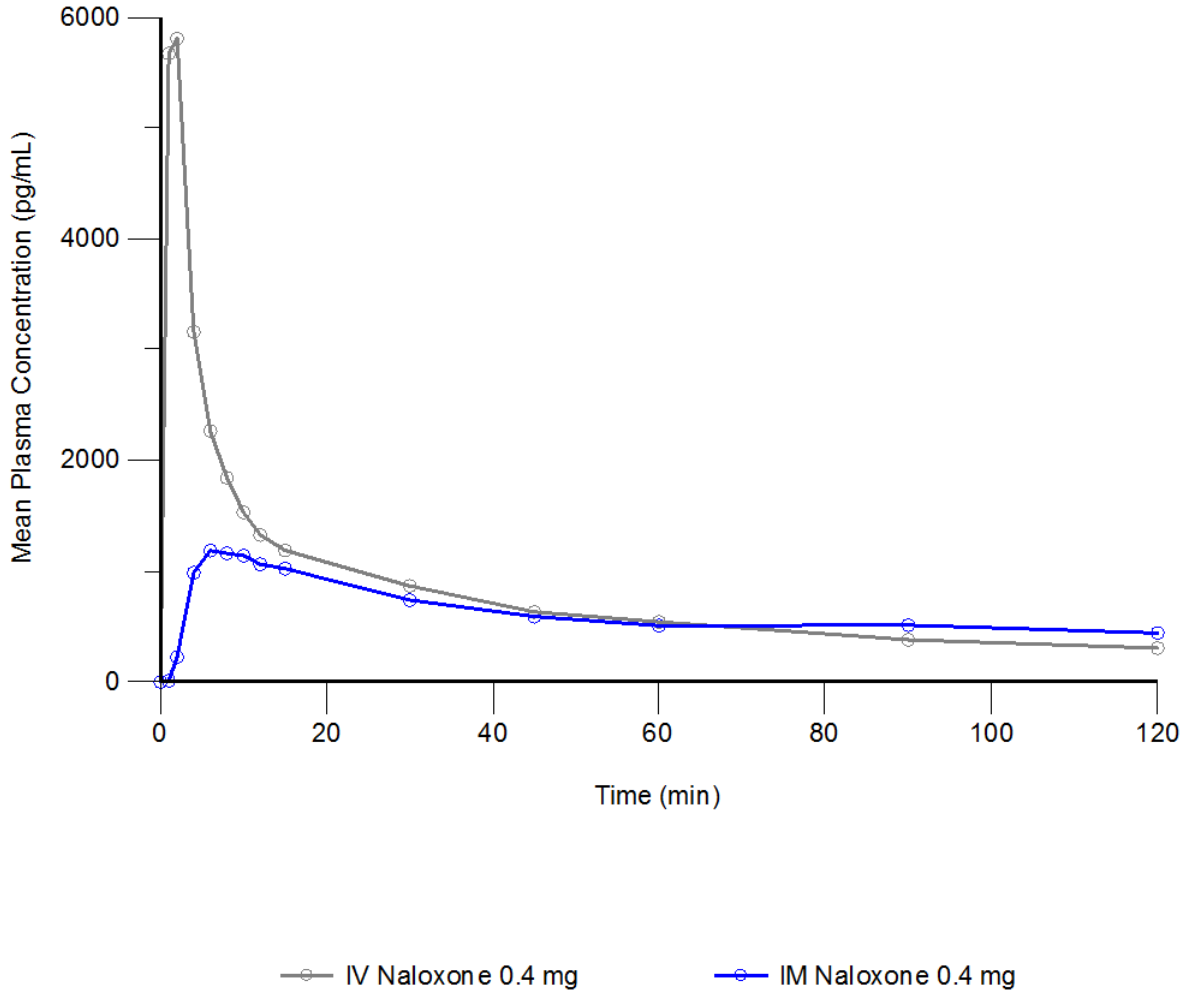

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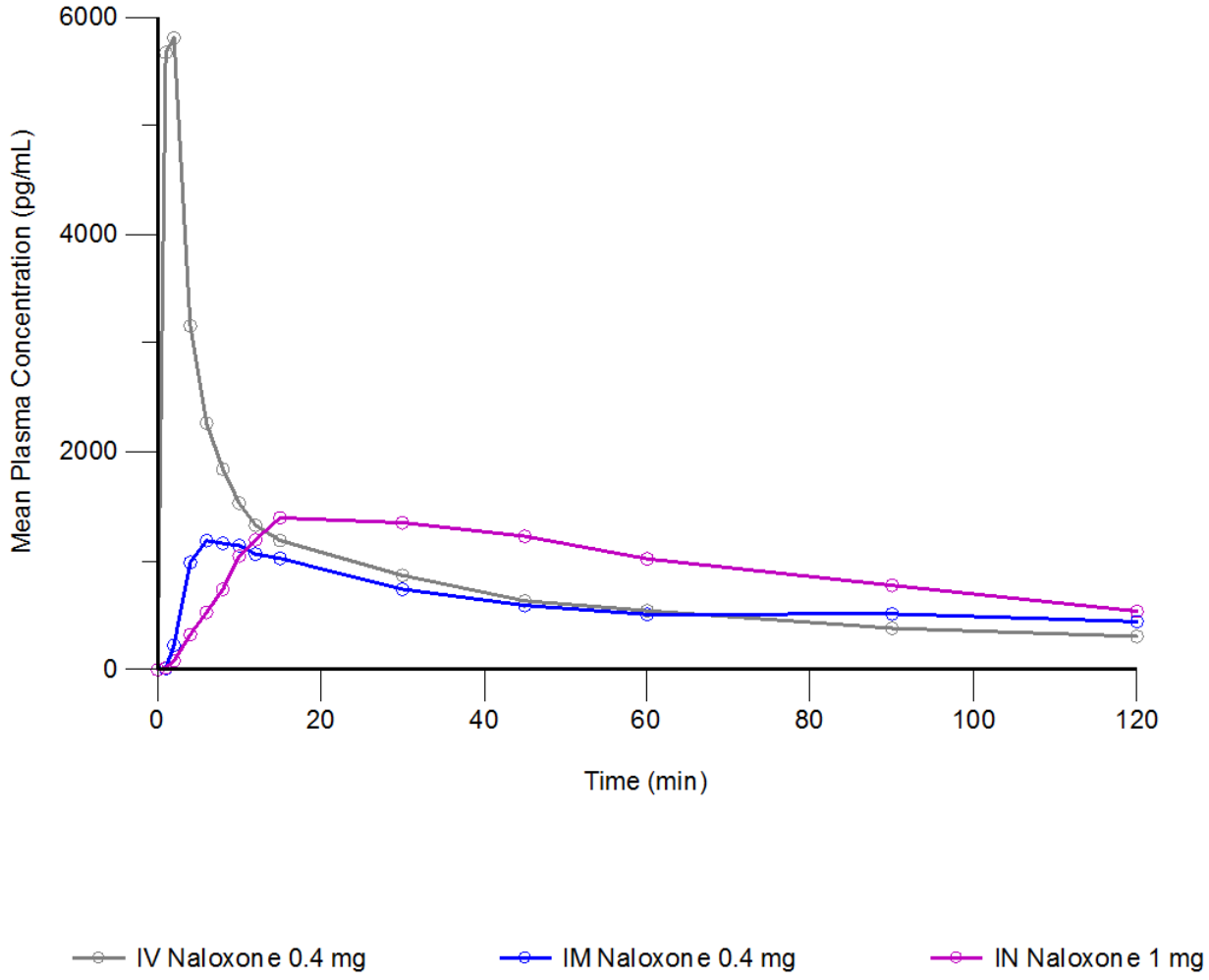

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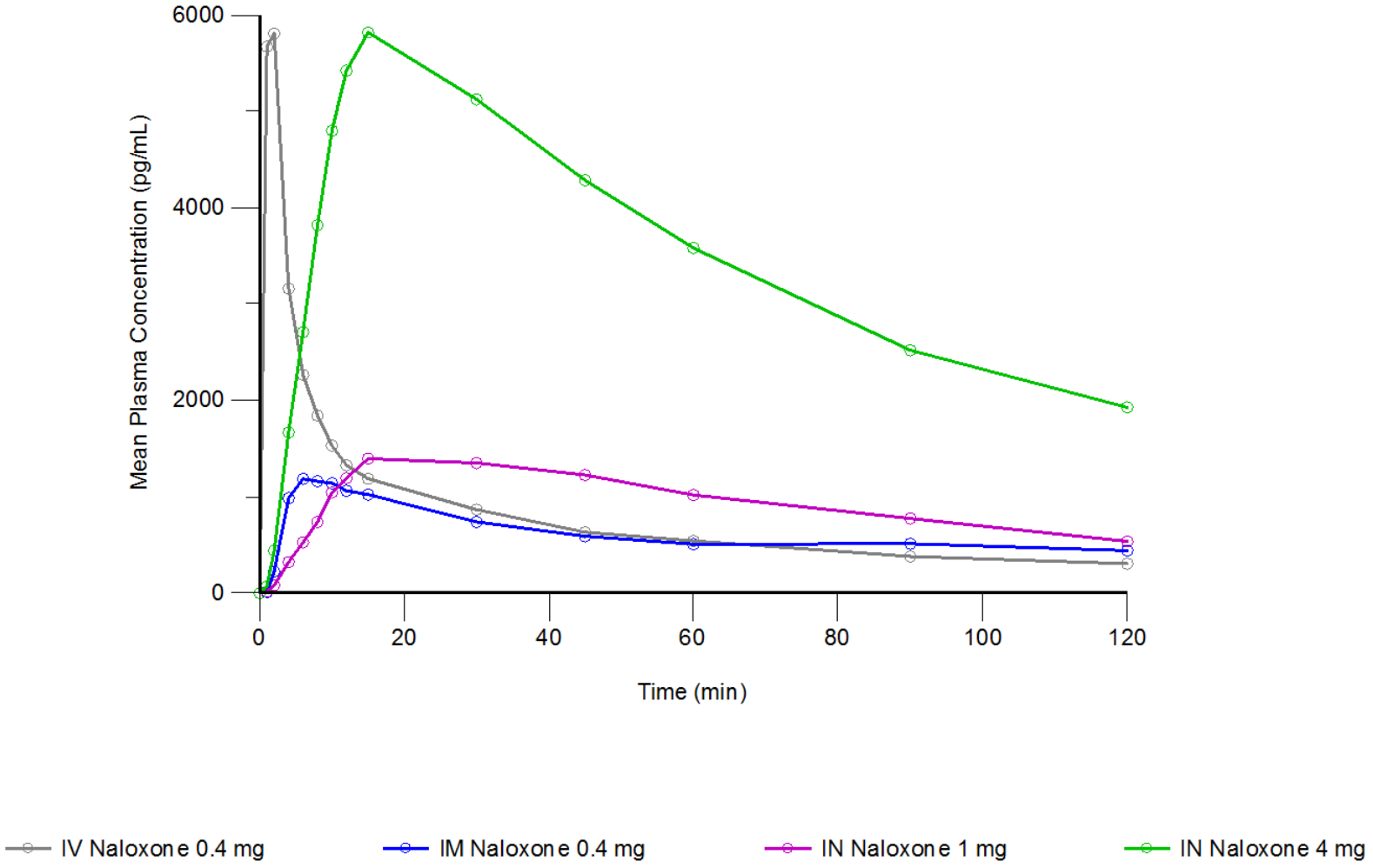

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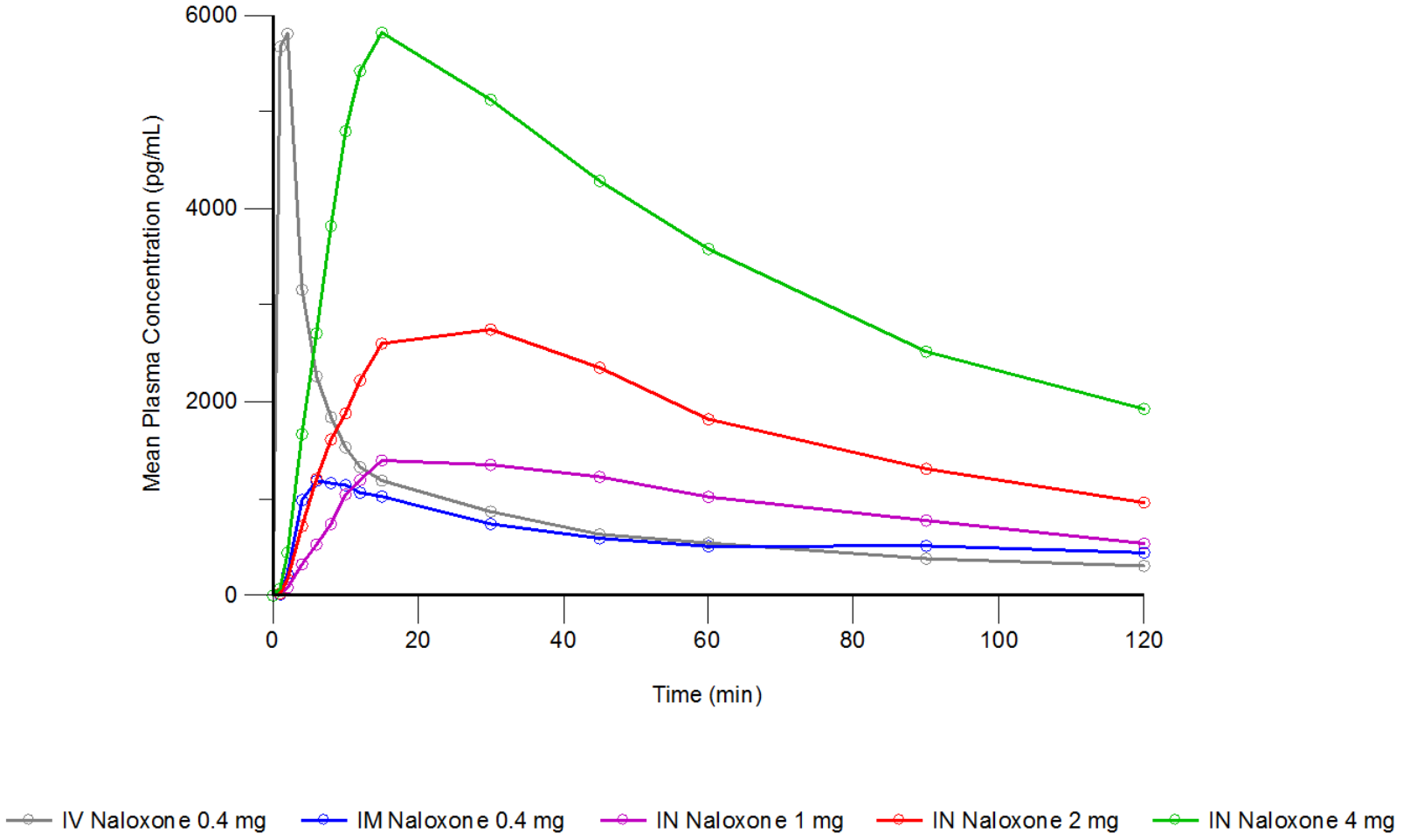

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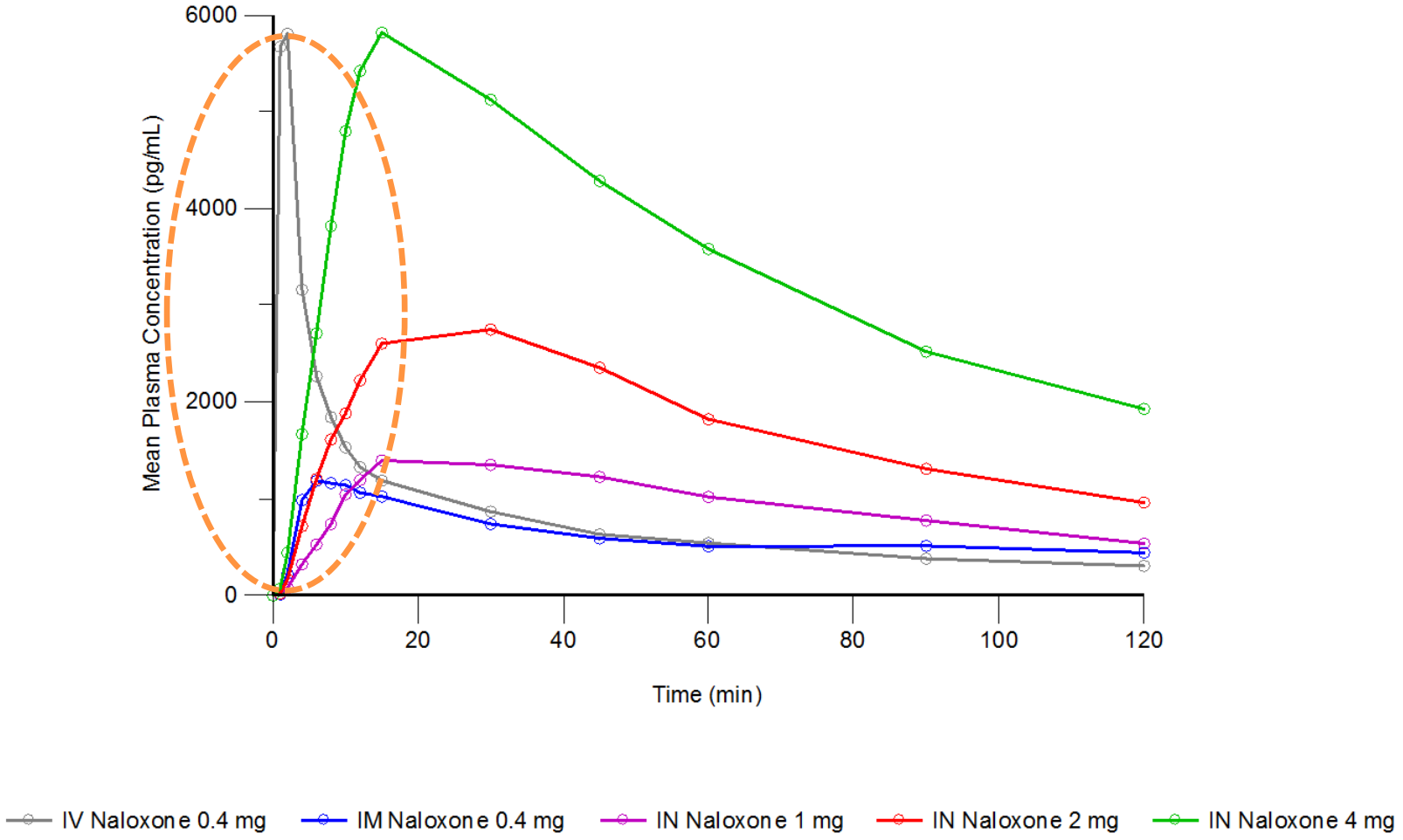

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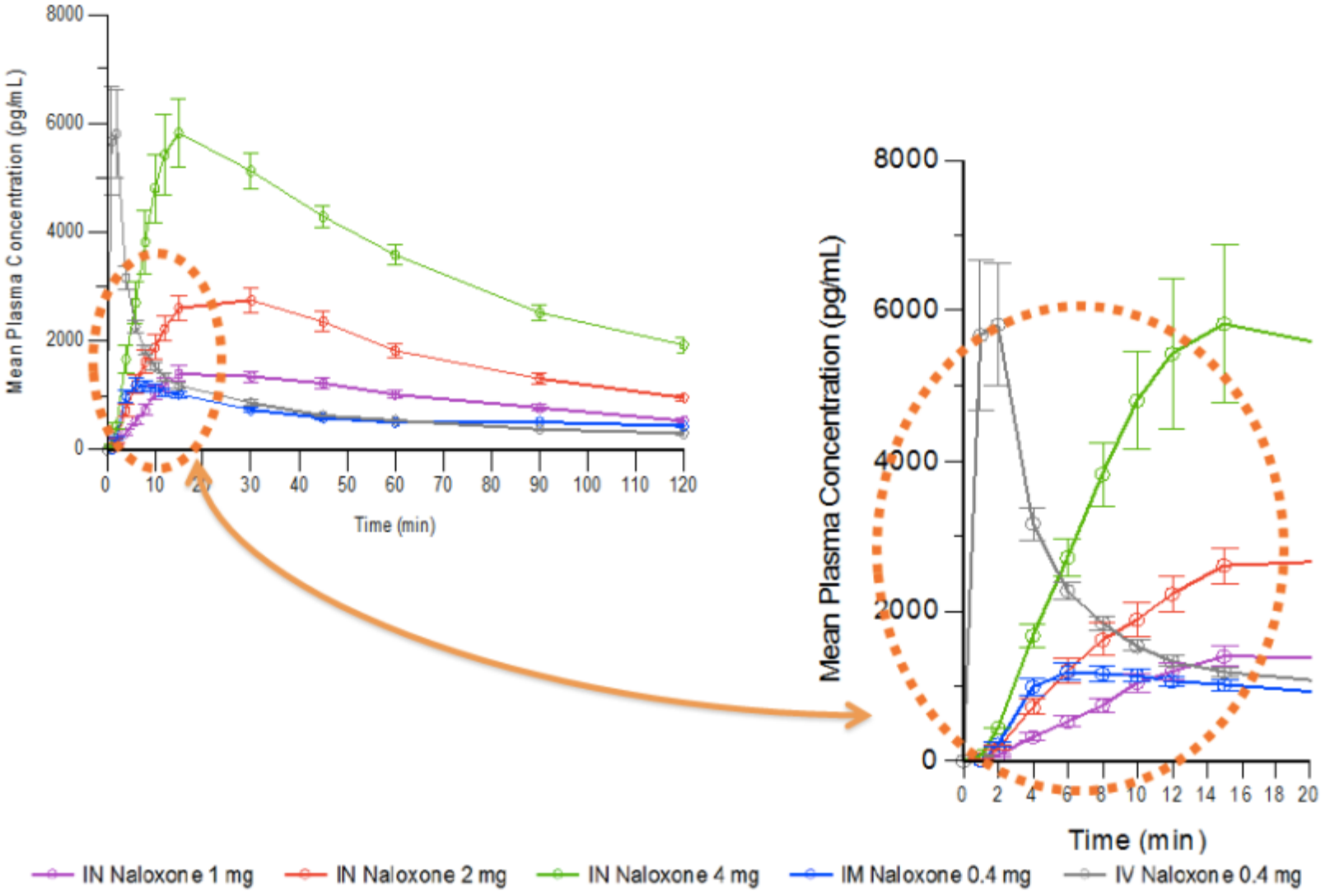

3.2 | Key findings: Bioavailability

	Ratio (%) 90% CI (lower, upper)		
	IN 1 mg	**IN 2 mg**	**IN 4 mg**
Absolute Bioavailability IN : IV*	**50 (44.6, 56.6)**	**47 (41.7, 52.6)**	**48 (43.3, 53.5)**
Relative Bioavailability IN : IM**	**51 (45.2, 57.1)**	**47 (41.7, 53.5)**	**48 (43.2, 54.1)**

*IV 0.4 mg used as the reference treatment for the comparison
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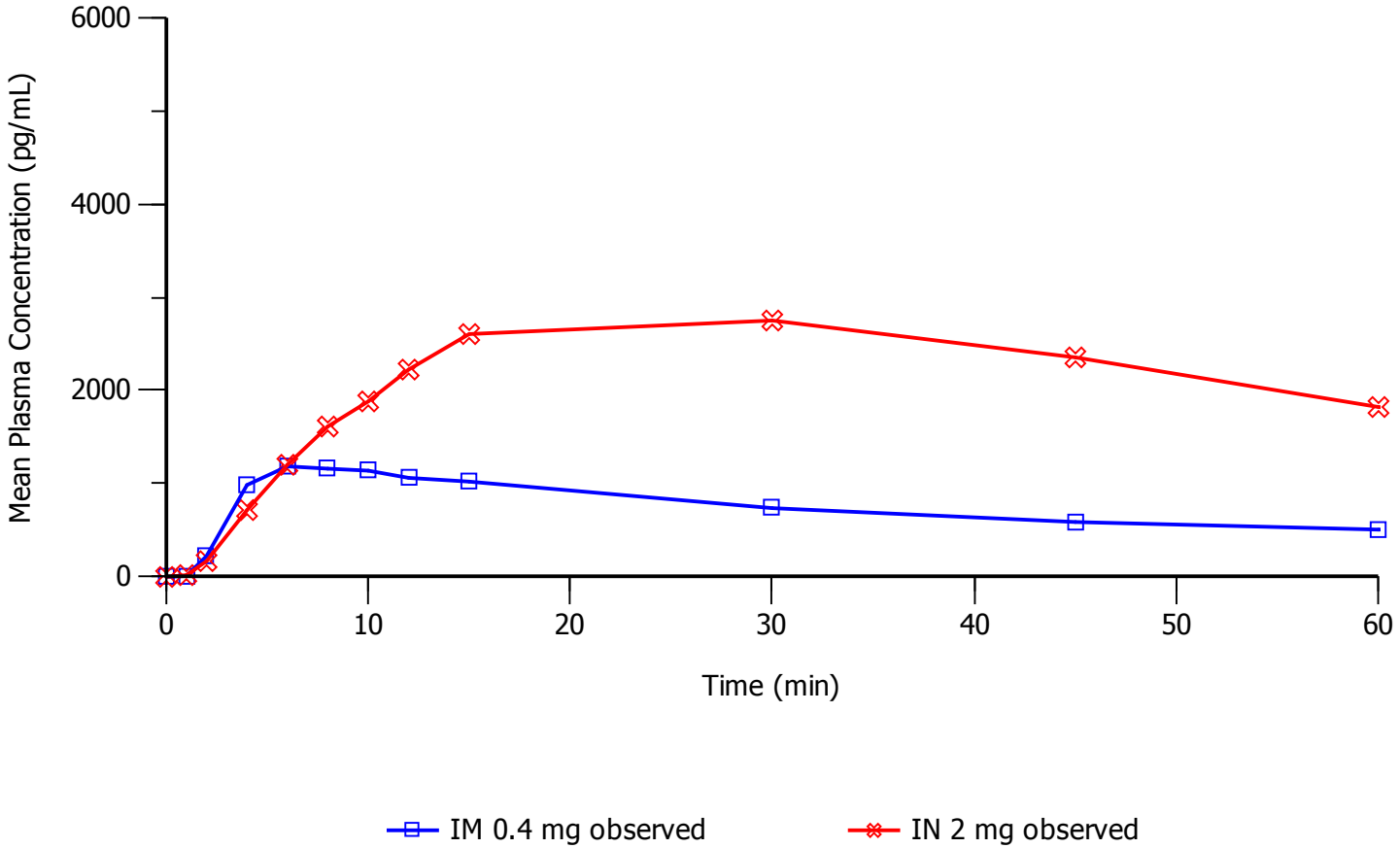
Relative Bioavailability IN : IM**	**51 (45.2, 57.1)**	**47 (41.7, 53.5)**	**48 (43.2, 54.1)**

IN = 50% X 2 X 2mg

IM = 100% X 5 X 0.4mg

*IV 0.4 mg used as the reference treatment for the comparison
**IM 0.4 mg used as the reference treatment for the comparison

3.3 | Key findings: Simulation of 2nd dose



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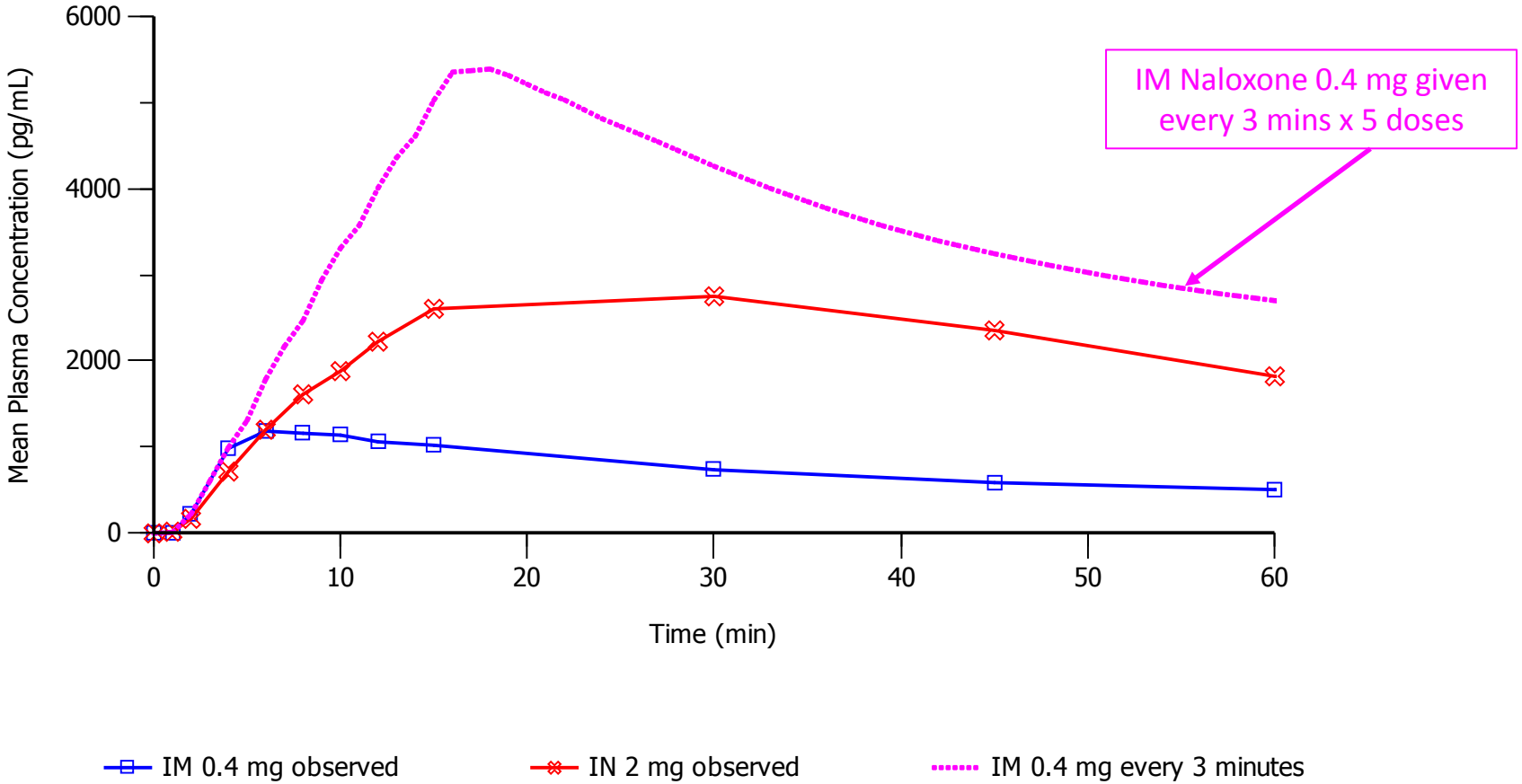

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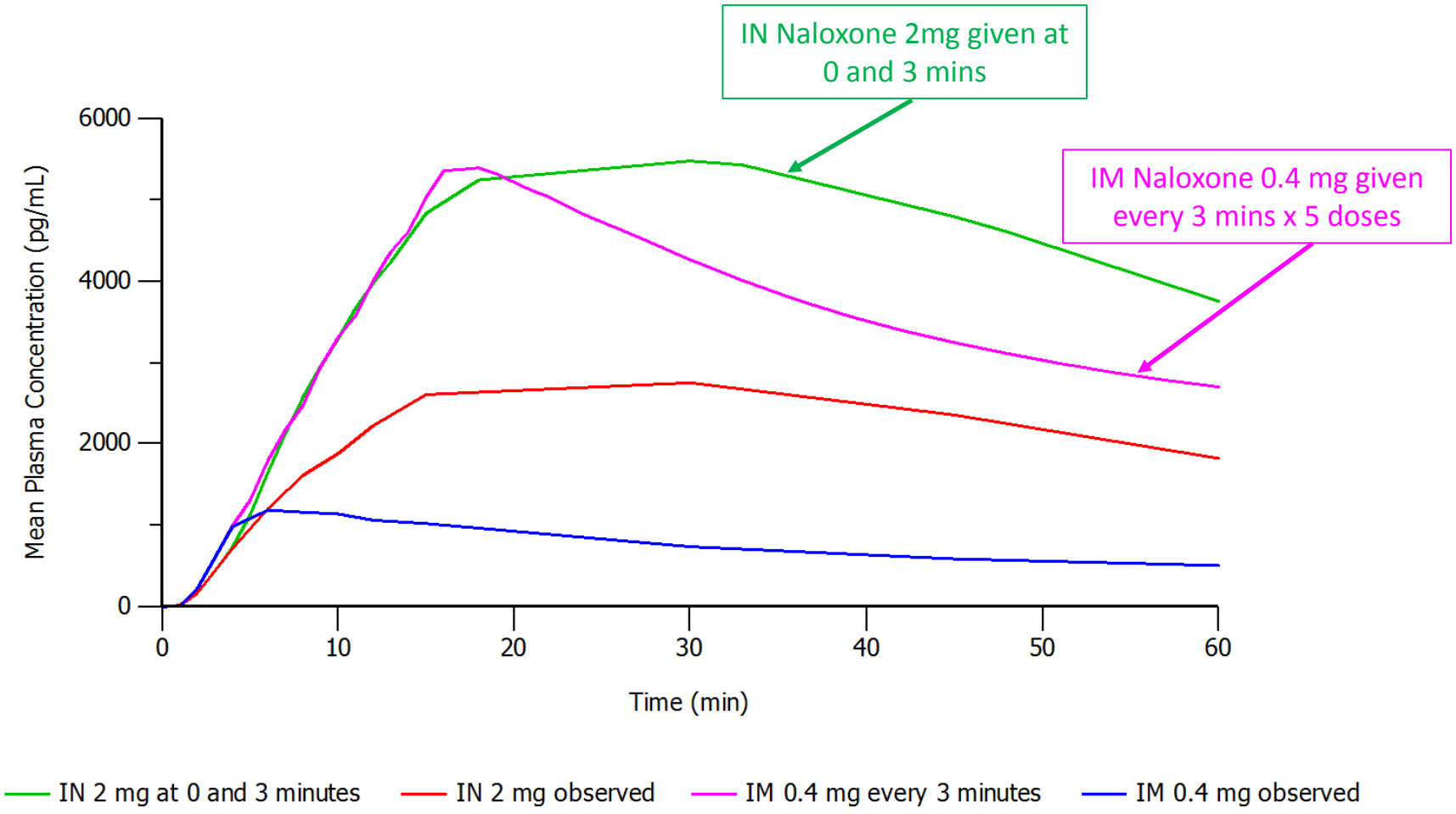

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4 | Implications for next studies

- Advantages and disadvantages of different curves:
  - 2mg IN dose gives speed of onset comparable to 0.4mg IM through the first 10 minutes – looks suitable for OD reversal?
  - 2mg IN ongoing plasma levels for the next 2 hours at twice the level maintained by the IM dose – reduces risk of rebound toxicity?
- Is IN dose titration possible, similar to IM (see simulation)?
- The extra factor: time to naloxone administration?

4 | Future clinical practice & policy

1) Is a 2mg/0.1mL naloxone nasal spray a viable alternative to 0.4mg IM injection?
2) Will nasal naloxone produce a better medium-term naloxone taper?
3) Will clinicians and policymakers find it easier to introduce IN naloxone?

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European Monitoring Centre
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INSIGHTS EN 20

Preventing opioid overdose deaths with take-home naloxone

Editors
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National Addiction Centre, Addictions Department, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom

EMCDDA project group
Dagmar Hedrich and Roland Simon

Photo credit: https://www.theguardian.com/world/picture/2016/oct/21/eyewitness-london-uk